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NEWS 14	FEB 22	Updates in EPFULL; IPC 8 enhancements added
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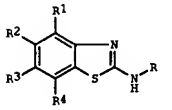
L7 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN

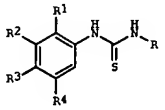
ACCESSION NUMBER: 2004:569886 CAPLUS
DOCUMENT NUMBER: 141:123657
TITLE: Cyclization process for substituted benzothiazole derivatives
INVENTOR(S): Spurr, Paul
PATENT ASSIGNEE(S): Switz.
SOURCE: U.S. Pat. Appl. Publ., 13 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004138465	A1	20040715	US 2003-743613	20031222
CA 2512361	AA	20040722	CA 2003-2512361	20031229
WO 2004060879	A2	20040722	WO 2003-EP14928	20031229
WO 2004060879	A3	20041118		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003300234	A1	20040729	AU 2003-300234	20031229
EP 1583752	A2	20051012	EP 2003-799511	20031229
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1738808	A	20060222	CN 2003-80108406	20031229
PRIORITY APPLN. INFO.:			EP 2003-48 A	20030107
			WO 2003-EP14928 W	20031229

OTHER SOURCE(S): CASREACT 141:123657; MARPAT 141:123657
GI



I

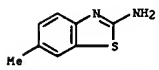


II

AB The present invention relates to a process for preparation of amino substituted benzothiazole derivs. of formula (I) [wherein R1, R2, R3 = H, lower alkyl, lower alkoxy, halogen; R4 = H, lower alkyl, lower alkyloxy, halogen, five or six membered non arom. heterocyclyl group unsubstituted or substituted by lower alkyl or an oxo-group, NR5R6 (wherein R5, R5 = H, lower alkyl, -C(O)-lower alkyl, -(CH2)nO-lower alkyl or benzyl, optionally substituted by lower alkyl, or NR5R6 is an five or six membered heteroaryl group); R1 and R2 or R2 and R3 may form together with the corresponding carbon atoms a ring contg. -OCH2O- or -CH:CH-CH:CH-; R = H or -C(O)R' (wherein R' = a five or six membered non arom. heterocyclyl group, five or six membered heteroaryl group or is aryl, which rings may be substituted by the groups selected from lower alkyl, halogen-lower alkyl, lower alkoxy, cyano, nitro, CHO, CO2H or by pyrrolidin-1-ylmethyl; n = 1-4)] or a pharmaceutically acceptable salt thereof, wherein the cyclization is carried out by the treatment of a N-phenylthiourea or N-phenyl-N'-acylthiourea derivs. of formula (II; R-R4 = same as above) with sulfoxide/HBr/solvent to give the desired products of formula I [R = H, C(O)R']. Thus, to a suspension of 15.0 g (43.7 mmol) N-[3-(3-benzoylthioureido)-4-methoxyphenyl]acetamide in 200 mL glacial acetic acid was added 7.65 mL (43.6 mmol) a 5.7 M soln. of HBr in acetic acid, and the mixt. was heated at 90° for 1 h. DMSO (2.5 mL, 48.0 mmol) was then added and the mixt. was heated at 90° for 1.5 h, cooled to room temp., and poured onto 1000 mL distd. water, stirred for 15 min, and then filtered, followed by washing the filter cake with water and then drying in vacuo at 50° to give 12.8 g (86%) N-(7-acetylamino-4-methoxybenzothiazol-2-yl)benzamide as a light brown solid.

IT **2536-91-6P**, 2-Amino-6-methylbenzothiazole
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of substituted benzothiazole derivs. by cyclization of N-phenylthiourea or N-phenyl-N'-acylthiourea derivs.)

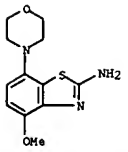
RN 2536-91-6 CAPLUS
CN 2-Benzothiazolamine, 6-methyl- (9CI) (CA INDEX NAME)



IT **383865-57-4P**, [4-Methoxy-7-(morpholin-4-yl)benzothiazol-2-yl]amine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of substituted benzothiazole derivs. by cyclization of N-phenylthiourea or N-phenyl-N'-acylthiourea derivs.)

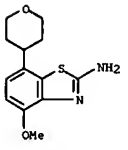
RN 383865-57-4 CAPLUS
CN 2-Benzothiazolamine, 4-methoxy-7-(4-morpholinyl)- (9CI) (CA INDEX NAME)

L7 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)

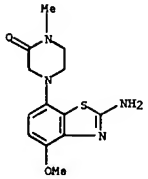


IT **554411-25-5P**, [4-Methoxy-7-(tetrahydropyran-4-yl)benzothiazol-2-yl]amine **722550-79-0P**, 4-(2-Amino-4-methoxybenzothiazol-7-yl)-1-methylpiperazin-2-one **722550-81-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of substituted benzothiazole derivs. by cyclization of N-phenylthiourea or N-phenyl-N'-acylthiourea derivs.)

RN 554411-25-5 CAPLUS
CN 2-Benzothiazolamine, 4-methoxy-7-(tetrahydro-2H-pyran-4-yl)- (9CI) (CA INDEX NAME)

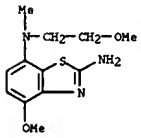


RN 722550-79-0 CAPLUS
CN Piperazinone, 4-(2-amino-4-methoxy-7-benzothiazolyl)-1-methyl- (9CI) (CA INDEX NAME)



RN 722550-81-4 CAPLUS
CN 2,7-Benzothiazolediamine, 4-methoxy-N7-(2-methoxyethyl)-N7-methyl- (9CI) (CA INDEX NAME)

L7 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)



L7 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1955:15976 CAPLUS
DOCUMENT NUMBER: 49:15976
ORIGINAL REFERENCE NO.: 49:3137a-i,3138a-i,3139a-i,3140a-i,3141a-i,3142a-i,3143a-i,3144a-i,3145a-i,3146a-i,3147a-i,3148a-i,3149a-i,3150a-i,3151a-b
TITLE: Oxazoles and oxazolones
AUTHOR(S): Cornforth, J. W.; Clarke, H. T.; et al.
CORPORATE SOURCE: Oxford Univ.;Princeton Univ. Press
SOURCE: Chemistry of Penicillin (1949) 688-848
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
GI For diagram(s), see printed CA Issue.
AB OXAZOLE SECTION: New methods for constructing the oxazole ring have been devised and the behavior of functional groups elucidated. The synthesis of oxazoles and imidazoles from K β-hydroxy-α-(α-alkoxyalkylideneamino)acrylates is given. A mixture of 51.1 g. AmCN and 24.5 g. EtOH was kept with 19.2 g. dry HCl below 0° for 2 wk, decomposed with 74 g. K2 CO3 in Et2O and distilled The crude AmC(OEt):NH (62.4 g.), b11 52-65°, was shaken with cold aqueous H2NCH2CO2Et.HCl for 1 h. The upper layer was fractionated to yield Et α-ethoxycaprylideneaminoacetate (I),b0.5 91°, saponified on gentle warming to AmCO2Et. The corresponding Me α-methoxycaprylideneaminoacetate (Ia), b0.1 74°, was similarly prepared A solution of 0.85 g. K in 2.5 g. EtOH and 14 g. Et2O was diluted to 50 mL. with Et2O, cooled to -15° and treated with a similarly cooled mixture of 4.85 g. I and 3.2 g. HCO2Et, yielding after 3 h. at -10°, 2.6 g. of hygroscopic needles of C5H11C(OEt):NC(CO2Et):CHOK (II). The corresponding K Me β-hydroxy-α(α-methoxycaprylideneamino) acrylate (IIa) was obtained in 3.2 g.-yield from 3.75 g. Ia. Treatment of 2.6 g. II and 1.25 g. DL-penicillamine in 5 cc. EtOH with alc.-HCl gave crystalline DL-N-caproylpenicillamine, m. 137-8°. Treatment of II with ethereal HCl produced Et 2-amyl-oxazole-4-carboxylate, b0.07 99° (dinitrophenyl-hydrazone, m. 165-6°; amide, m. 152°) saponified to 2-amyl-oxazole-4-carboxylic acid, m. 92-3° (PhNH2 salt. m.98.5-9.5°) readily decarboxylated to 2-amyl-oxazole, b. 172-3°; picrate, m. 84.5-5.5°. This general synthesis of 2-substituted oxazoles and their 4-carboxylic acids has been extended to Et 2-phenyloxazole-4-carboxylate, m. 69-70°, the corresponding acid, m. 209°, and carried through to the known 2-phenyloxazole. The method can be also applied to the synthesis of imidazoles. Treatment of I with aqueous NH4OH gave 2-amylimidazole-4-carboxylic acid, m. 230° (decomposition); with MeNH2.HCl or alc. H2NCH2CO2Et.HCl, I produced, resp., Et 2-amyl-1-methylimidazole-4-carboxylate (III), m. 42-3°, and Et 2-amylimidazole-4-carboxylate-1-acetate (IIIa), m. 61°. Similarly, Ia gave Me 2-amyl-1-methylimidazole, m. 66.7°, and Me 2-amylimidazole-4-carboxylate-1-acetate, m. 107°. Hydrolysis of III and IIIa yielded 1-methyl-2-amylimidazole-4-carboxylic acid, m. 121-3°, and 2-amyl-4-carboxyimidazole-1-acetic acid, m. 132-4°. Starting from PhCH2CN, Et 2-benzylimidazole-4-carboxylate-1-acetate, m. 111-2°, was likewise prepared, converted by treating with MeOH into a Me Et ester. On heating with aqueous NH4OH and with PhNH2, 2-amyl-oxazole-4-carboxylic acid was converted into 2-amylimidazole, m. 33-4° and 1-phenyl-2-amylimidazole, m. 143-4°. Synthesis of

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oxazoles by rearrangement of oxazolones. The Na salt of 2-benzyl-4-hydroxymethylene-5-oxazolone (2.7 g.) in 50 mL. abs. MeOH was treated with 5 mL. abs. Et2O contg. 0.38 g. HCl. The gummy product (2.28 g.) was taken up in 10 mL. abs. MeOH and heated for 30 min. with 6.2 mL. H2O contg. 0.42 g. NaOH. The residue on evapn. was dissolved in 10 mL. of iced H2O, acidified with dil. HCl to pH 6.5 and extd. with Et2O, yielding 700 mg. 2-benzyloxazole-4-carboxylic acid, m. 158°. On heating at 220°, crude 2-phenyl-4-(α-hydroxyethylidene)-5-oxazolone rearranged to 2-phenyl-5-methyloxazole (IV), m. 184-5° (decompn.). Similarly, on heating to 230°, Na 4-hydroxymethylene-g-amyl-5-oxazolone rearranged to 2-amyl-oxazole-4-carboxylic acid. Evapn. of 2-(1-pentenyl)-4-(hydroxymethylene)-5-oxazolone in NaOH and fusion of the residue at 250° under reduced pressure yielded 2-pentenyl-oxazole-4-carboxylic acid, m. 145-7°. Incidental syntheses of oxazole derivs. The action of PhSO3Ag on Me thiobenzylpenaldate di-Et acetal produced colorless prisms of 2-benzyloxazole-4-carboxylic acid, m. 156-7° and the dehydration of Et α-benzylamino-acetoacetate gave Et 2-phenyl-5-methyloxazole-4-carboxylate, m. 51-2°, hydrolyzed to the acid, m. 180-1°, decarboxylated at 220° in the presence of a trace of CuO to IV. Thus a reaction known to succeed with α-acylamino ketones and carboxylic esters is extended to β-keto esters. The 2-substituted oxazoles and their 4-carboxylic acids and esters are feebly basic, readily oxidized by cold aq. KMnO4 but stable to Br in CCl4. The ring opens on warming with 2,4-(O2N)2-C6H3NHNH2 in 2N HCl with a tendency to formation of glyoxal osazone derivs. Rosenmund redn. of 2-amyl-oxazole-4-carboxylic acid chloride produced 2-amyl-oxazole-4-carboxaldehyde, b8 108° (2,4-dinitrophenylhydrazone, m. 172-3°), converted by warming with D-penicillamine-HCl in AcOH to the thiazolidine, devoid of antibiotic properties. From the corresponding Et ester, 2-benzyl-4-carboxyoxazole hydrazide, m. 81-3° and benzylamide, m. 121-2° were prepd. In attempts to synthesize the thiazolidine-oxazolone structure for penicillin, attention was directed to the prepn. of 5-alkoxyoxazoles and many variations of the general method of dehydrating α-acylamino esters with P2O5 were introduced. By the use of PCl5, P2O5, POCl3, SOCl2, and PhSO2Cl, the following new oxazoles were prepd. (substituent given): 2-Ph, 5-MeO, b9 141°; 2-Ph, 5-PhCH2O, m. 56°; 2-PhCH2, 5-EtO, b15 152-4°; 2-PhCH2, 5-MeO, m.31-2°; 2-Am, 5-EtO, b0.8 82-5°; 2-Am, 5-MeO, b1.0 60-65°; 2-(1-C5H9), 5-EtO, b20 125-8° (C5H9 = pentenyl); 2-(1-C5H9), 5-MeO, b15 108-10°; 2-PhCH:CH, 5-EtO, m. 35°; 2-PhCH:CH, 5-Ph CH2O, picrate, m. 135° (decompn.); 2-Ph, 4-Me, 5-EtO, b10 151°; 2-Ph, 4-Me, 5-PhCH2O, picrate, m. 112-13°; 2-PhCH2, 4-Me, 5-EtO, b15 145-50°; 2-Am, 4-Me, 5-EtO, b3 92°; 2,4-Ph2, 5-EtO, m. 47-8°; 2-Ph, 4-PhCH2, 5-EtO, picrate, m. 105°; 2-Ph, 4-PhCH2, 5-PhCH2O, picrate, m. 117°; 2,4-(PhCH2)2, 5-EtO, b0.3 145-50°; 2-Am, 4-PhCH:CH, 5-EtO, m. 92°; 2-Ph, 4-CO2Et, 5-EtO, m. 75°; 2-Am, 4-CO2Et, 5-EtO, b0.1 122-5°; 2-(1-C5H9), 4-CO2Et, 5-EtO, b0.2 125°; 2-PhCH2, 4-CO2Et, 5-EtO, b0.1 165°. The possibility of converting an alkoxyoxazole to the corresponding oxazolone was realized by the catalytic hydrogenation of 2 g. of 2-phenyl-5-benzyloxyoxazole in 30 mL. dry dioxane in the presence of Pd-black to 2-phenyl-5-oxazolone, m. 91°. The converse reaction, transformation of an oxazolone to an alkoxyoxazole, has also been achieved. Methylation of 3 g. of 2-phenyl-4-carbethoxy-5-oxazolone with

L7 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)
500 mg. CH2N2 in 50 mL. Et2O yielded 2-phenyl-4-carbethoxy-5-methoxyoxazole, m. 72°. Similarly, methylation of 2-phenyl-4-carbomethoxy-2-oxazolin-5-one gave 2-phenyl-4-carbomethoxy-5-methoxyoxazole, m. 98°, identical with that prepd. by the dehydration of BzNHCH(CO2Me)2 with PCl5 in CCl4. Attempts to obtain 5-alkoxyoxazole-4-carboxaldehydes covered a wide range. Formylation of BzNHCH2CO2Et and condensation with PhCH2NH2 in Et2O gave Et β-benzylamino-α-benzamidoacrylate, R'NHCH:C(CO2Et)NHCOR (V; R = Ph, R' = PhCH2), m. 108°, cyclized by PBr3, POCl3 or PCl5 to 2-phenyl-4-benzylaminomethylene-5-oxazolone (VI), m. 134-7; Ac deriv., m. 140°. In the same way, Et β-benzylamino-α-phenylacetamido acrylate (VIa) with PBr3 gave 2-benzyl-4-benzylaminomethylene-5-oxazolone (VIb). Dehydration of Et α-benzamido-β,β-diethoxypropionate with PCl5-POCl3 yielded 2-phenyl-4-(ethoxymethylene)5-oxazolone (VII). Distn. of benzyl α-benzamido-β,β-diethoxypropionate gave a mixt. of products including benzyl α-benzamido-β-ethoxyacrylate, m. 108-10°; benzyl 2-phenyloxazole-4-carboxylate, m. 106-7°; and VII. Attempts were made to cyclize α-benzyl-β-methyl-DL-phenylpenicilloate, HN.CH(CO2R').CMe2.S.CHCH(NHCOR)CO2CH2Ph (VIII, R = Ph, R' = Me) (VIIIa), m. 130°; dibenzyl-DL-phenylpenicilloate (VIII, R = Ph, R' = PhCH2) (VIIIb), m. 107-8°; and DL-2-(carboxy-1-hexenoylaminomethyl)-5,5-dimethyl-4-carbometh-oxythiazolidine benzyl ester (VIII, R = 1-pentenyl, R' = Me). (VIIIc). The action of PCl5 on VIII and VIIIa gave definite evidence of formation of thiazolidinylalkoxyoxazoles and cyclization of VIIIb and chromatog. purifn. of the product gave benzyl 2-(2-phenyl-5-benzyloxy-4-oxazolyl)-5,5-dimethylthiazolidine-4-carboxylate, m. 120-5°, absorption band at 2850 A. This reduced in EtOAc using a Pd-BaSO4 catalyst with 2 mol H, corresponding to removal of 2 PhCH2 groups, yielded a product with no-antibiotic activity. The simpler thiazolidines were also investigated. The reaction of 3-methyl-2-(benzamidocarbethoxymethyl)-thiazolidine with PCl5 gave a Cl-contg. product, converted by NaHCO3 to a probable sulfoxide. With PCl3, a product was obtained, which was converted by aq. KOH to 2-phenyl-4-hydroxymethylene-5-oxazolone. β-Methylaminoethyl mercaptan-HI (from 15 g. of-2-methylthiazoline-MeI) in 20 mL. H2O was treated with 11 g. of crude Na salt of C,N-diformylglycine Et ester and neutralized with AcOH. After 15 h., NaHCO3 was added and the dried CHCl3 exts. (120 mL.) were concd. to give 6.55 g. of crude product, converted by treatment with 65.5 mL. of 10% HCl in EtOH to 4.4 g. of 2-(aminocarbethoxymethyl)-3-methylthiazolidine-2HCl (IX), m. 169-70° (decompn.). IX (10.0 g.) in 36.1 mL. of 2N NaOH and 35 mL. EtOH was stirred with 6.6 g. PhCH2CS2Me for 45 h., yielding 6.2 g. of colorless prisms of 2-[(phenylthioacetamido)carbethoxymethyl]-3-methylthiazolidine (X), m. 100-100.5°. Addn. of 5.0 g X in 20 mL. CHCl3 to 8.6 g. PhSO3Ag and 2.5 mL. pyridine in 70-mL. CHCl3 gave no identifiable org. products. The action of PhSO3Ag on Me α-phenylthioacetamido-β,β-diethoxypropionate yielded a product from which Me-benzylpenaldate and 2-benzyloxazole-4-carboxylic acid were isolated. By the PCl5 method it has been possible to prep. 4-(2-thiazolyl)-2-benzyl-5-ethoxyoxazole and 2-(p-nitrophenyl)-4-(5,5-dimethyl-4-carbomethoxy-2-thiazolinyl)-5-ethoxyoxazole. Attempts to introduce a CHO group into the 4-position of 2-phenyl-5-ethoxyoxazole (XI) using PhNMeCHO and POCl3 gave 2-phenyl-4-anilinomethylene-5-oxazoline. With AcNHBr, XI gave 2-phenyl-4-bromo-5-ethoxyoxazole, b0.8 128°. The oxidn. of 2-phenyl-4-methyl-5-ethoxyoxazole with SeO2, CrO3 or CrO2Cl2 resulted only in far-reaching breakdown. Condensation of PhCH2CH2COCO2H with AcNH2 or AmCONH2 gave α-acetamido- and α-caproyl-amino-γ-phenylisocrotonic acid (XII). Treatment of the Et ester of XII

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with PCl5 afforded 2-amyl-4-styryl-5-ethoxyoxazole (XIII), disrupted by ozonization with prodn. of BzOH and H2NCOCO2Et. XIII (5.7 g.) in 100 mL. glacial AcOH was stirred with 9.0 g. of Pb(OAc)4 for 3 h., yielding 6.1 g. of 2-(1-acetoxyamyl)-4-styryl-5-ethoxyoxazole, m. 90-1°, degraded by distn. with loss of AcOH to 2-(1-pentenyl)-4-styryl-5-ethoxyoxazole (XIV), m. 100°, reduced catalytically to XIII. Oxidn. of 2.83 g. XIV in 30 mL. tert-BuOH contg. 0.75 g. H2O2 and 30 mg. OsO4 at 40-50° for 2 h. produced PrCHO and 5-ethoxy-4-styryl-oxazole-2-carboxaldehyde, m.130.5°, converted into the thiazolidine, m. 169°, using DL-penicillamine. Cyclization of AmCONHCH(CO2Et)2 in dry alc. free CHCl3 with PCl5, yielded 2-amyl-5-ethoxyoxazole-4-carboxylic acid (XIV), m. 63.4°, which on refluxing with PCl5 in CHCl3 gave Et 2-amyl-5-chlorooxazole-4-carboxylate (XV), b0.3 106°, catalytically reduced over Pd-BaSO4 in xylene to 2-amyl-oxazole-4-carboxylate, acidified to the free acid (XVa), m. 93-4°, converted by alc. EtONa to XIV. Treatment of 2 g. XVa with 1.09 g. PCl5 in 10 mL. CHCl3 and distn. produced the corresponding acid chloride, b0.3 96°, converted by (NH4)2CO3 in aq. NH4OH to the amide, m. 90°, which, distd. with P2O5, gave 2-amyl-5-chloro-4-cyanooxazole (XVb), b0.15 72°. Redn. of 3.0 g. XVb in a suspension of 5.7 g. anhyd. SnCl2 in 40 mL. dry ether yielded unstable 2-amyl-5-chloro-oxazole-4-carboxaldehyde (XVI) (dinitrophenylhydrazone, m. 109-10°), rearranging in 3 days at room temp. or on low pressure distn. to 2-amyl-oxazole-4-carboxylic acid chloride. Despite its instability, XVI readily combined with D-penicillamine-HCl to produce D-2-(2-amyl-5-chloro-4-oxazolyl)-5,5-dimethylthiazolidine-4-carbo-xylic acid-HCl, m. 150-2° (decompn.). A similar series of compds. starting with Et 2-phenyl-5-ethoxyoxazole-4-carboxylate (XVII) and proceeding to the thiazolidine was later prepd. XVII was sapond. to the cryst. acid (XVIIa), m. 148°, converted to the acid chloride (XVIIb), m. 105-6°, and to Et 2-phenyl-5-chlorooxazole-4-carboxylate, m. 68°, by refluxing in xylene for 1 h. The corresponding acid (XVIII), m. 178-4° (decompn.), was converted through the acid chloride, m. 118-20°, the amide, m. 183°, and the cyano compd., m. 112°, to 2-phenyl-5-chlorooxazole-4-carboxaldehyde (XIX), m. 91-3°. The addn. of 1.14 g. aldehyde in 5 mL. EtOH and 10 mL. Et2O to 0.93 g. D-penicillamine-HCl in 5 mL. H2O and 0.65 g. AcONa, and passage of HCl through a filtered ethereal soln. of the reaction product, yielded 1.5 g. of 2-(2-phenyl-5-chloro-4-oxazolyl)-5,5-di- methylthiazolidine-4-carboxylic acid-HCl, m. 178° (decompn.); Me ester-HCl, m. 120-2°; free acid, m. 166°; Me ester, m. 154°; PhCH2 ester, m. 116-7°. The thiazolidine exhibited a low order of antibiotic activity. A similar series of 2-benzyloxazole derivs. have been prepd. but the corresponding thiazolidine was inactive: 2-benzyl-5-ethoxy-oxazole-4-carboxylic acid, m. 118° (decompn.); Et ester, b0.1 165°; acid chloride, m. 81-2°; 2-benzyl-5-chlorooxazole-4-carboxylic acid, m. 183° (decompn.); Et ester, b0.02 170-5°; acid chloride, m. 156-7°; cyano compd., m. 49-50°; aldehyde [dinitrophenylhydrazone, m. 173°; semicarbazone, m. 185° (decompn.)]; 2-(2-benzyl-5-chloro-4-oxazolyl)-5,5-dimethylthiazolidine-4-carbo-xylic acid-HCl, m. 176-7° (decompn.). By refluxing 223 mg. XVIII in 3 mL. EtOH with 40 mg. Na, the Cl was replaced by the EtO group with formation of the corresponding acid, XVIIa. Distn. of the aldehyde XIX at 0.1 mm. gave 2-phenyloxazole-4-carboxylic acid chloride, m. 107-8°, transformed by stirring with cold concd. aq. NH4OH to the amide. Similarly the acid chloride XVIIb was converted to the amide, m. 118-19°, rearranged by heating for a few min. at 140° to Et 2-phenyl-5-aminooxazole-4-carboxylate, m. 183deg;. All oxazoles found to undergo rearrangement may

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be formulated as 5-substituted oxazoles having a CO group in the 4-position, the general case being N:CR'.O.CR3:CCOR2 → N:CR'.O.CR2:CCOR3. Known examples of rearrangement are tabulated. Since the mol. is unstable when R3 and R2 are Et and Cl, resp., or when R3 and R2 are Cl and H, resp., it is deduced that the ethoxy aldehydes should show too great stability for successful synthesis. Cyclization of AmCONHCHCNCO2Et with P2O5 in CHCl3 gave 2-amyl-4-cyano-5-ethoxyoxazole, b0.03 98°, not reduced to the aldehyde by SnCl2 in Et2O. No 4-acetyloxazole was obtained from the MeMgI reaction product but the isolation of Et α-caproylaminoacetoacetate (dinitrophenylhydrazone, m. 166-7°) indicated oxazole ring cleavage. The dehydration of 2-phenyl-5-ethoxyoxazole-4-carboxyamide with POCl3 or the ethylation with MeCHN2 of the crude oxazolone obtained by treating BzNHCHCNCO2H with Ac2O produced 2-phenyl-4-cyano-5-ethoxyoxazole, m. 77°. The previously unknown 5-aminooxazoles were prepd. thus: treatment of 7 g. BzNHCH(CN)CO2Et, m. 138°, in 125 mL. CHCl3 with 6.2 g. PCl5 gave 4.5 g. Et 2-phenyl-5-aminooxazole-4-carboxylate, m. 185°, also prepd. by the action of POCl3 on Bz-NHCH(CONH2)CO2Et. Condensation of 1.18 g. HZNCH-(CO2Et)2 with 1.13 g. PhNHOEt by heating for 30 min. at 110° gave the alternative compd., formulated as 2-phenyl-4-carbethoxy-5-imidazolone, m. 275°. Similarly were prepd. Et 2-benzyl-5-aminooxazole-4-carboxylate (XX), m. 124° and the corresponding 2-benzyl-4-carbethoxy-5-imidazolone, m. 254° (decompn.); 2-(1-pentenyl)-4-carbethoxy-5-aminooxazole, m. 105°; 2-amyl-4-carbethoxy-5-aminooxazole (XXa), m. 104° and the corresponding 2-amyl-4-carbethoxy-5-imidazolone., m. 230° (decompn.). On heating at 170° for 5 min., XXa was entirely converted into AmCONHCH(CN.)CO2Et, m. 83°. Heating either XX or PhCH2CONHCH(CN)CO2Et at 160-70° for 15 min. produced an equil. mixt. with the open chain ester predominating. This same mixt. was formed by heating 2-benzyl-5-ethoxyoxazole-5-carboxylic amide, probably through initial rearrangement to the aminooxazole. Stirring 35 g. NCCH2CO2CH2Ph in 40 mL. of chilled glacial AcOH with satd. aq. NaNO2 (16.5 g.) yielded 29 g. NCC(NOH)CO2CH2Ph, m. 119°, reduced with Al-Hg to NCC(NH2)CO2CH2Ph, m. 95°, and benzoylated to NCCH(NHBz)CO2CH2Ph, m. 130°, converted by heating at 160° for 5 min. to 2-phenyl-4-carbobenzyloxy-5-aminooxazole, m. 203°. The 4-carbethoxy-5-aminooxazoles are feebly basic substances whose HCl salts dissoc. readily. XXa.HCl, on boiling with ethereal EtOH gave AmCONHCH(CONH2)CO2Et, m. 150-1°, along with NH4Cl. Treatment of 1 g. XXa in 10 mL. dry Et2O at -15° with NOCl gave a low yield of Et 2-amyl-oxazole-4-carboxylate, m. 92-3°. Formylation of 15 g. BzNHCH2CN in 200 mL. HCO2Et and 100 mL. benzene by addn. of NaOEt (from 2.16 g. Na) in 100 mL. benzene produced, after treatment of the intermediate BzNHC(:CHONa)CO2H with dil. H2SO4 to pH 4, 2-phenyl-5-aminooxazole-4-carboxaldehyde (XXI), m. 172-3°, probably in the tautomeric form. Formylation of AmCONHCH2CN and distn. of the product yielded 2-amyl-oxazole-4-carboxylic acid amide, m. 154-5°, evidently by rearrangement of XXI. The action of POCl3 on Bz-NHCH(CONH2)2 and AmCONHCH(CONH2)2, m. 231°, gave 2-phenyl-5-amino-4-cyanooxazole, m. 233° (Ac deriv., m. 202-3°), and 2-amyl-5-amino-4-cyanooxazole, m. 117°. These aminooxazoles could not be reduced to aldehydes.
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Satn. of 0.52 g. PhCH2CSNHCH(CN)CO2Et, m. 157°, treated in 5 mL. dry EtOH with dry HCl at -10° and the soln. evapd. after 12 h. at 20° in vacuo yielded 0.5 g. 2-benzyl-4-carbethoxy-5-aminothiazole, m. 180°. OXAZOLONE SECTION. Part. I. General Chem. of Oxazolones. Prepn. of 2-Oxazolin-5-ones. The reaction of Ac2O with α-acylamino acids is the most general procedure by which new oxazolones, O.CR:N.CR1R2.CO, have been prepd. (substituents given): 2-Me, 4-iso-Pr, b10 60°; 2-PhCH2, 4-Me, b0.5-1.0 122-3°; 2-PhCH2, 4-iso-Pr, b0.5 115-17°; 2,4-(PhCH2)2, oil; 2-Am, 4-PhCH2, b5 135-8°; 2-(2-pentenyl), 4-PhCH2, b1.0 155-7°; 2-PhCH2, 4,4-Me2 (I), m. 59.5°; 2-Ph, 4-iso-Bu, m. 56-7°; 2-PhCH2, 4-sec-Bu, b2.0 137-9°; 2-Ph, 4,4-C5H10, m. 71°; 2-PhCH2, 4-Me, 4-PhCH:CH, m. 56-7°; 2-Ph, 4-CO2Et, m. 147-8°; 2-Am, 4-CO2Et, oil; 2-Ph, 4-(p-MeOC6H4CH2); 2-PhCH2, 4-(p-MeOC6H4CH2); and 2-PhCH2, 4-iso-Bu. Similarly, heating 100 g. BzNHCH2CO2H (II) in 300 mL. Ac2O at 100° yielded 49 g. 2-phenyl-2-oxazolin-5-one (III), m. 94-5°, the only monosubstituted oxazolone prepd. by this method. By warming BzNHCHPhCH2CO2H in CHCl3 with 1 equiv. of 2-benzyl-4-methyl-5-oxazolone, a good yield of 2-phenyl-4-benzyl-5-oxazolone, m. 68-9°, was obtained. Addn. of 1 g. NaNO2 in 20 mL. H2O to 3 g. of BzNHC(CONHNH2):-CHPh in 30 mL. N HCl gave α-benzamidocinnamic azide, m. 113-4° (decompn.), converted on boiling with EtOH or treatment with pyridine at room temp. to 2-phenyl-4-benzylidene-5-oxazolone (IV). Similarly, Me2C:C(NHBz)-CON3 was converted to 2-phenyl-4-isopropylidene-5-oxazolone (IVa). These type II (unsatd. substituent at the 4-position) unsatd. oxazolines are formed more readily than the above-listed type I (satd. substituent at the 4-position) satd. oxazolones to which the azide conversion could not be extended. Redn. of IV over Pd-C gave 2-phenyl-4-benzyl-5-oxazolone (V), m. 67-8°. IVa was similarly reduced in dioxane to give an oil which, treated with PhNH2 in benzene, produced Me2CHCH(NHBz)CONHPh, m. 211-2°. The possibility arose that any reagent capable of transforming an acid to its chloride might be expected to convert an α-acylamino acid to the corresponding oxazolone. Thus treatment of II in 15 mL. dioxane with 2 mL. PBr3 gave III. Similarly, 14.5 g. PhCH2CONHCMe2CO2H in 150 mL. dioxane was treated with 18 g. PBr3. The solid product suspended in dioxane and treated with slight excess of CH2N2 in ether yielded I, converted by PhCH2NH2 into PhCH2CONHCMe2CONH2, m. 122-3°. Treatment of PhCH2CHNHBzCO2H in pyridine with PBr3 likewise gave the known V. Attempts to prep. 2-benzyl-5-oxazolone from PhCH2CONHCH2CO2H gave an unstable oil, converted by PhCH2NH2 into PhCH2CONHCH2CONHCH2Ph. Conversion of PhCH:C(NHBz)CO2H into IV was effected by POCl3, SOCl2, pyridine, by ClCH2COCl and K2CO3, and by AcCl in dioxane. Oxazolones have been produced by treating PhCH2OCOCl with acylamino acids. Apart from direct dehydration, three methods are known for the prepn. of type II oxazolones; the Erlenmeyer aldehydeacylglycine synthesis, the Bergmann-Stein reaction of N-(α-haloacyl)amino acids with Ac2O, and the dehydration of β-hydroxy-α-acylamino acids. In that III reacts with Me2CO in the presence of NaOAc to yield IVa in the absence of Ac2O, it is suggested that III is an intermediate in the Erlenmeyer synthesis. In the presence of a little pyridine, BzH condenses with III to produce IV. Similarly, 2-phenyl-4-propylidene-5-oxazolone, m. 88-9°, was obtained in good yield from III and EtCHO. By adding Ac2O dropwise with stirring to 17.9 g. II and 6.1 g. fused NaOAc in 580 mL. Me2CO, refluxing for 3-4 h. at 59-62°, pouring the reaction mixt. over 200 g. ice and dilg. to

1500 mL. produced high yields (73%) of relatively pure 2-phenyl-4-isopropylidene-5-oxazolone, m. 98°. Condensation of II with (EtO)2CHCHO and Ac2O gave 4,4'-glyoxalidenebis(2-phenyl-5-oxazolone), m. 325° (decompn.). Though no acyl interchange in the Erlenmeyer synthesis occurs with II, the formation of 2-methyl-4-benzylidene-5-oxazolone occurs when either PhCH2CONHCH2CO2H or AmCONHCH2CO2H (VI) is refluxed with BzH in the presence of Ac2O and NaOAc. Refluxing VI (15.1 g.) with 13.1 g. AmCO2Na and 61 g. (AmCO)2O in 49 mL. Me2CO for 24 h. at 75° gave α-caproyl-amino-β,β-dimethylacrylic acid, m. 162-3°, converted by melting and heating in vacuo at 180-90° into 2-amyl-4-isopropylidene-5-oxazolone, b0.03 60-2°. By Bergmann's method, 2-methyl-4-isopropylidene-5-oxazolone (VII) and 2-methyl-4-sec-butylidene-5-oxazolone were prepd. from Me2CHCH2CH(NHCOCH2Cl)CO2H and EtMeCHCH-(NHCOCH2Cl)CO2H. Carter's method was used to prep. VII by the action of Ac2O on Me2C(OMe)CHNH2CO2H. Ring opening Reactions of Oxazolones. The general reaction of oxazolones with H2O, ROH, RSH, NH3, RNH2 and RR'NH represented by O.CR:N.CR1R2.CO + HX → OCRHNCR1R2COX, suggested originally the thiazolidine-oxazolone formulation of penicillin. Comparison of the reactivity of V with that of IV showed the former to be rapidly hydrolyzed by 2N aq. acid or alkali under conditions not affecting the latter. V reacts with ROH more rapidly than III. In the presence of NaOMe or PhCH2NMe3-OH, IVa was converted quant. to Me2C:C(BzNH)CO2Me, m. 130-1°. The methanolysis of 2-benzyl-4-p-methoxybenzyl-5-oxazolone in dry abs. MeOH yielded (N-phenylacetyl-p-methoxyphenylalanyl)-p-methoxyphenylalanine, m. 199-200°. The formation of the dipeptide may be due to an "ortho-ester" reaction with the imino-ether form of the oxazolone. Reaction of PhCH2SH with III and I yielded benzyl hippurate, m. 101-2° and Me2CHCH(NHCOCH2Ph)COSCH2Ph, m. 138.5°. Almost all types of oxazolones react with PhCH2NH2 to form α-acylaminoacyl-benzylamides. The reaction of V with d-MePhCHNH2 in dry dioxane was followed polarimetrically and at const. rotation, produced N-benzoylphenylalanine-d-N-α-phenylethylamide, m. 178-80°, [α]D23 28.5° (c 1, dioxane). The strongly enolyzed 2-phenyl-4-carbethoxy-5-oxazolone formed a salt with PhCH2NH2, converted on heating in xylene to the benzylamide, m. 132°. The reaction of PhNH2.HCl with III and 2-benzyl-4-sec-butyl-5-oxazolone gave the normal anilide and the corresponding acid. Reaction of V and 2-phenyl-4-isobutyl-5-oxazolone with L-HSCH2CH-(NH2)CO2Me produced the normal amides, m. 128-9°, and 131-5°, resp., the NH2 group taking precedence over the SH group in the condensation. The action of N2H4 on oxazolones has been clarified. The addn. of 18 g.-phenyl-4-methyl-5-oxazolone to excess 60% N2H4.H2O in EtOH and heating to 50-60° for 30 min. gave 17.5 g. benzoylalanine hydrazide, m. 142-4°; benzylidene deriv., m. 193-4°. Treatment of IV with N2H4.H2O also gave the normal hydrazide, PhCH:C(NHBz)CONHNH2, m. 113-14°, converted by heating the corresponding azide in xylene to 2-oxo-4-benzylidene-6-phenyl-1,3,5-oxadiazine, m. 174° (decompn.). Conversion of Me2C:C(NHBz)CON3 similarly produced 2-oxo-4-isopropylidene-6-phenyl-1,3,5-oxadiazine, m. 166-8°. A mixt. of 5 g. IV, 10 mL. N2H4.H2O and 3 mL. EtOH was refluxed for 30 min. yielding 4-benzamido-3-phenyl-5-pyrazolidone, m. 228-9°, identical with the product formed by refluxing PhCH:C(NHBz)CONHNH2 (VIII), m. 157-8°, which N2H4.H2O for 30 min. Similarly, the hydrazide Me2C:C(NHBz)CONHNH2, m. 192-4°, was converted into 3,3-dimethyl-4-benzoylamino-5-pyrazolidine, m. 106-8°. The hydrazide VIII was boiled in N NaOH